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"Case Study Of Metastatic Malignant Phyllodes: Unveiling The Critical Role Of Adjuvant Treatment Post Breast-Conserving Surgery"

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Abstract:
This case study explores the trajectory of a 56-year-old female diagnosed with metastatic malignant phyllodes tumour following breast-conserving surgery (bcs) in a non-oncological setup in 2021. Lacking adjuvant treatment and information on the necessity of oncologist consultation, the patient defaulted follow-up. Subsequently, metastases in the lung, paravertebral region, spine, and subcutaneous tissues developed. The case underscores the critical importance of informed decision-making post-bcs to prevent metastatic progression. The patient received palliative radiotherapy to the right paravertebral mass and c-spine compression, resulting in symptomatic relief. Palliative chemotherapy, specifically six cycles of adriamycin based, was initiated alongside symptomatic treatment. This comprehensive approach led to improved power in both upper limbs, pain relief, and a decrease in the size of subcutaneous nodules. The patient, now two months post-treatment, continues to do well upon follow-up.

Key words: *phyllodes tumour, malignant, case study, treatment modalities, metastatic*

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I. Introduction:

Phyllodes tumours (pts) represent rare neoplastic entities, characterized by the interplay of stromal and epithelial components, comprising merely 0.3%-1% of breast tumours in women [1]. Coined from the greek term "phyllodes," meaning leaf-like, the name encapsulates the distinctive papillary projections discerned through pathological examination. Originally termed "cystosarcoma phyllodes" by johannes müller in 1838 [2], the world health organization (who) later formalized their classification in the breast tumour spectrum, elucidating diagnostic criteria and grading. The classification categorizes pts into benign (60%-75%), borderline (15%-20%), or malignant (10%-20%), relying on the evaluation of five pivotal features: stromal cellular atypia degree, mitotic activity per 10 high-power fields (hpfs), tumour margins (infiltrative or circumscribed), presence of stromal overgrowth, and the nature of the tumour border [3]. Typically ranging from 4 to 5 cm, pts surpassing 10 cm are termed "giant" pts, constituting about 20% of all pts [4].

Historically, a case in 1931 unveiled the malignant potential of pts with lung metastases [5]. Contemporary literature reports malignancy in 10%-15% of pts, with 9%-27% of malignant phyllodes tumours

demonstrating distant organ metastasis, frequently to lungs, bones, brain, and liver [6]. The prognosis for breast pts exhibiting recurrence or metastasis is grim, with survival estimates falling below 2 years post-diagnosis [7-10]. This overview provides a foundation for comprehending the varied spectrum of pt behaviour and sets the stage for a focused exploration of a unique case featuring metastatic malignant phyllodes. Our case study delves into the intricacies of a unique presentation -metastatic malignant phyllodes. In contrast to the common trajectory, this case underlines the challenges and successes encountered in managing this rare and aggressive entity, contributing valuable insights to the broader understanding of pt behaviour. Additionally, we provide a review of the literature surrounding pts, shedding light on their varied clinical manifestations and treatment modalities.

II. Case presentation:

A 56-year-old female resident of north lakhimpur presented with a history of a breast lump persisting for 6 months. Subsequently, in december 2021, she underwent wide local excision (wle) for the breast lump. The histopathological examination revealed a malignant phyllodes tumour with a tumour size of 6.5 cm and the closest margin of 0.2 cm at elsewhere, however, despite the close margin, a complete mastectomy was not performed, and no revisions were made. Furthermore, the patient did not receive any adjuvant treatment, seek consultation from an oncologist, and remains unaware of her current medical status and prognosis. Unfortunately, 2 years later, the patient presented with severe pain over the right chest, radiating to the back and right upper limb. A contrast enhanced ct chest revealed a 7.3x6.6x4.1 cm (fig 1) lesion in the right lung upper lobe posterior segment, along with multiple soft tissue nodules in both lungs. A noteworthy finding was a 6x5 mm skeletal lytic area in the c5 vertebra. Ct-guided biopsy from the right lung mass was done.

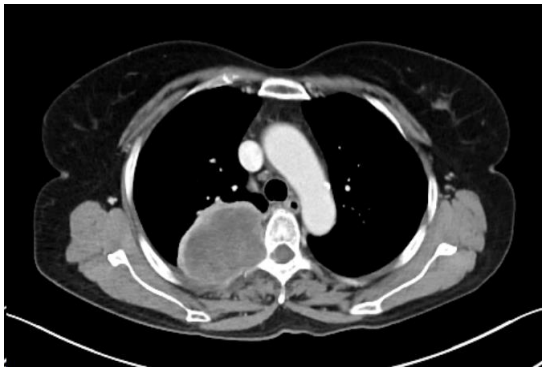

Fig. 1: contrast-enhanced ct chest image showing a 7.3x6.6x4.1 cm lesion in the right lung upper lobe posterior segment.

Pathological findings confirmed a high-grade spindle cell neoplasm, with immunohistochemistry showing gata3 positivity and cd34 negativity, indicating metastasis from the primary breast neoplasm (fig 2,3,4). The patient's general condition was good, but her ecog performance status was iii, with tenderness over the right chest wall and sternum on examination.

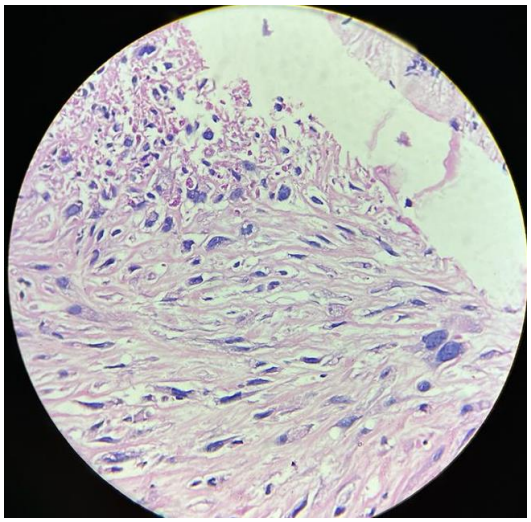

Fig 2 showing spindle cells having pleomorphic nuclei and presence of tumour necrosis on top left corner, on h&e staining.

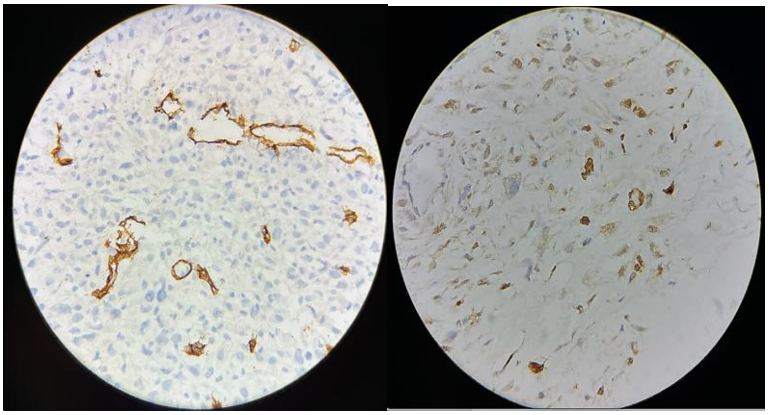

Fig 3 showing tumour cells are cd34 negative on cd34 ihc
fig 4 showing tumour cells are ihc positive on gata3 ihc

Palliative radiation (30gy/10 fractions) to right paravertebral lesion and pain management with opioids were initiated, along with supportive measures. In july and august 2023, the patient completed the prescribed palliative radiation regimen of 30gy in 10 fractions. Subsequently, after 15 days, there was a notable decrease in pain over the chest wall. However, the patient experienced a new symptom of severe pain over the neck and upper back, radiating to the left upper limb. On examination, there was a notable decrease in power in the left upper limb (3/5) and the right upper limb (4/5). Mri c-spine findings revealed altered signal intensity involving the c6 and c7 vertebral bodies and posterior elements, along with a soft tissue component causing neural foraminal stenosis at c5-c6, c6-c7, and c7-d1 levels, indicative of metastases (fig 5,6). Additionally, altered signal intensity at d3, d4, d5, and d12 correlated with previous ct findings. The patient underwent another round of palliative radiation to the cervical spine (30gy/10 fractions) until september 2023, in conjunction with supportive medications. Continuous physiotherapy for both hands was advised, and the patient was kept on opioids under monitoring. Eventually there was significant improvement in power, with the left upper limb now at 4/5 and the right upper limb at 5/5. Subsequently, the patient was planned and initiated on palliative chemotherapy with doxorubicin (adriamycin) 60 mg/m² and cyclophosphamide 600 mg/m² every 3 weeks for 6 cycles, with 3 weekly blood counts monitoring.

After the first cycle of chemotherapy, the patient developed non-tender subcutaneous nodules over the anterior abdominal wall. Despite this, chemotherapy continued, and remarkably, the nodules disappeared before completing the last (6th) cycle. Following the chemotherapy course, power improved completely, and pain over the chest wall decreased. Post-chemotherapy, the patient has been on follow-up and, after 2 months, reports a significant relief of symptoms. She is currently on conservative management, and opioids were discontinued after the second palliative radiation and before the initiation of chemotherapy. The positive response to treatment is encouraging, and ongoing follow-up is essential to monitor the patient's progress and address any emerging concerns. Hopeful for continued well-being in the future.

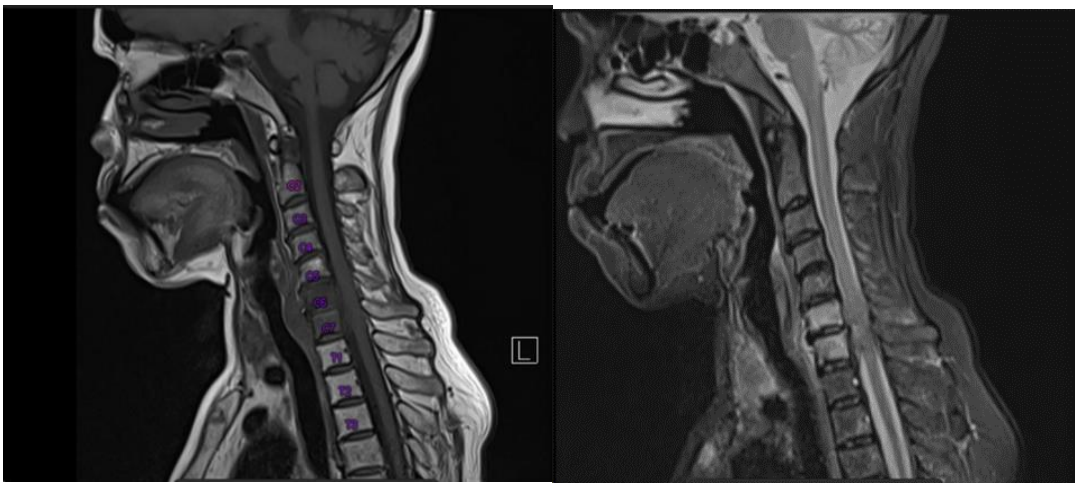

Fig 5,6. Sagittal sections of the mri showing altered signal intensity involving the c6 and c7 vertebral bodies and posterior elements with soft tissue component, causing neural foraminal stenosis at c5-c6, c6-c7, and c7-d1

III. Discussion:

Phyllodes tumours of the breast represent rare fibroepithelial neoplasms with a diverse range of clinical behaviours. Distinguishing between phyllodes tumours (pt) and fibroadenomas (fa) is crucial despite their shared fibroepithelial nature, as their management significantly differs. While fas can often be safely monitored without further intervention, pts necessitate surgical excision. A multidisciplinary approach is essential for accurate differentiation in patients with diagnosed fibroepithelial lesions. The literature documents rare instances of fas transforming into pts, highlighting the complexity of their pathology. There are two plausible explanations for a core biopsy-proven fa being later identified as a pt. The first possibility involves misdiagnosis at the core biopsy stage due to the overlapping pathologic features of these lesions. The second, albeit rarer, possibility is the progression of a fa into a pt [11]. Unfortunately, there are no definitive imaging or clinical predictors for anticipating such transformations. Pts predominantly affect women between 35 and 55 years old, while fas are the most common solid breast masses in women under 30 but can also occur in older age groups [11]. In men, phyllodes tumours are usually associated with gynecomastia, with pts being rarely reported [12].

Genetic syndromes, such as li-fraumeni syndrome linked to germline tp53 mutations, can contribute to the development of pts. This syndrome is associated not only with breast cancers but also with brain tumours, soft tissue sarcomas, and occasionally other tumour types [13]. Malignant pts pose a higher risk of metastatic disease, whereas benign and borderline tumours tend to exhibit local recurrence with a rare incidence of metastasis [14].

Research by koh et al. [15] indicated that a combination of a large tumour size (≥90 mm) and the presence of malignant heterologous elements significantly correlates with the development of distant metastasis. The most common sites for metastasis in malignant pts include the lung, bones, brain, and liver [7-10]. Uncommon metastatic sites reported in literature encompass the adrenal glands, kidney, skin, ovary, heart, pleura, oral cavity, duodenum, pancreas, tonsillar, and para-aortic nodes (16-25). Once patients with malignant pts develop metastasis, their prognosis becomes exceedingly poor, with median survival ranging from 5 to 30 months [26].

Surgery stands as the primary treatment modality for breast phyllodes tumours (pts). A recent meta-analysis by lu et al. [27], encompassing 54 retrospective studies with 9234 patients, revealed that positive surgical margins significantly increased the risk of local recurrence: 8% for benign, 13% for borderline, and 18% for malignant pts. Jang et al. [28], in a retrospective review of 164 patients with pts, identified the presence of tumour cells on the resection margin as a key prognostic factor for local recurrence. Interestingly, they found that the width of the resection margin did not influence the risk of local recurrence.

The most recent guidelines from the national comprehensive cancer network (nccn) 2023, recommend local surgical excision for the treatment of pts, with tumour-free margins of 1 cm or greater recommended for malignant and borderline pts. Notably, narrow surgical margins do not categorically mandate mastectomy; total mastectomy is only considered if lumpectomy or partial mastectomy fails to achieve a margin width of ≥1 cm. For benign pts, excisional biopsy involves complete mass removal without the explicit goal of obtaining specific surgical margins. Importantly, as phyllodes tumours rarely metastasize to axillary lymph nodes (alns), surgical axillary staging or aln dissection is generally deemed unnecessary unless there are pathologic lymph nodes on clinical examination [13]. These guidelines underscore the importance of tailoring the surgical approach based on the specific characteristics and pathology of the phyllodes tumour.

The role of radiotherapy in the management of malignant phyllodes tumours (pts) remains a subject of ongoing debate, with no current consensus on its utility. The national comprehensive cancer network (nccn) guidelines suggest considering radiotherapy for malignant pts specifically in the context of local recurrence, supported by level 2 b evidence [13]. However, barth et al. [29], in a prospective, multi-institutional study, demonstrated that margin-negative resection coupled with adjuvant radiotherapy proves highly effective in achieving local control for borderline and malignant phyllodes tumours. A meta-analysis by chao et al. [30], encompassing 17 retrospective studies with 696 patients, further supports the efficacy of radiotherapy in attaining local disease control and preventing metastasis. Additionally, belkacemi et al. [31] reported a significant reduction in the local recurrence rate with radiotherapy in 159 patients with malignant and borderline phyllodes tumours. This evidence suggests that margin-negative resection combined with adjuvant radiotherapy could emerge as a new standard of care for borderline and malignant pts.

The application of adjuvant chemotherapy in the treatment of pts is hindered by the lack of robust data from large prospective studies. In cases of distant metastasis to the lungs, the most common chemotherapy regimen identified in our literature review involved doxorubicin and ifosfamide [7, 9, 32,33,34]. Adjuvant chemotherapy was omitted in six studies [35-40], either due to its controversial effects or patient preference. Moon et al. [10] reported complete remission of lung metastasis three years after mastectomy, axillary lymph node dissection, and adjuvant chemotherapy with doxorubicin and ifosfamide. Another study by koukourakis et al. [9] indicated that a combination of cisplatin with nab-paclitaxel and liposomal doxorubicin chemotherapy exhibited acceptable toxicity and high effectiveness in eradicating metastatic lesions. The comprehensive cancer network (nccn) guidelines recommend treatment for distant metastasis in pts based on the nccn soft tissue sarcoma clinical practice guidelines version 2.2023. However, the overall lack of consensus and paucity of large-scale

prospective studies underscore the need for further research to establish clear guidelines for the use of adjuvant radiotherapy and chemotherapy in the management of malignant phyllodes tumours.

There is a paucity of data available in the form of case reports elucidating the outcomes and prognosis of patients afflicted with malignant phyllodes tumours (pts) exhibiting distant metastases. This subgroup of pts manifests aggressive behaviour and necessitates a more assertive approach to management through multimodality therapy. Predisposing factors encompass malignant histology, considerable tumour size (>10 cm), and instances of local recurrence following inadequate surgical resections. Pathologically, these tumours are characterized by heightened mitotic rates, stromal hypercellularity, atypia, and infiltrating margins, mirroring the features observed in our patient who developed paravertebral lung lesion 2 years after primary wide local excision.

Metastases may histologically resemble the primary tumour, yet the presence of mesenchymal components, such as osteosarcomatous, chondrosarcomatous, or rarely liposarcomatous patterns intertwined with epithelial components, has also been documented [41,42]. The emergence of the sarcomatous component within phyllodes tumours is attributed to the metaplastic potential of myoepithelial cells in the breast, contributing to the clinical and pathological heterogeneity observed in patients.

Distant metastases may manifest either synchronously or emerge several months or years, with instances exceeding a decade, following the primary diagnosis. In one series of patients, one patient presented with bone metastases 13 years after the initial tumour diagnosis [43]. While chemotherapy plays a limited role and is predominantly administered for palliative purposes in the metastatic setting, it primarily addresses the stromal elements, necessitating a therapeutic strategy akin to managing soft tissue sarcomas. Commonly employed chemotherapeutic agents include ifosfamide, cisplatin, etoposide, or doxorubicin [44]. Recent studies have explored the role of molecular analysis and molecular targeting agents, such as tyrosine kinase inhibitors, along with the utilization of taxanes in the management of metastatic malignant pts [44]. Genomic changes, specifically in tp53 and nras, have been correlated with the malignant potential of pts [44]. Once metastasis ensues, the prognosis becomes markedly grim, with very few patients surviving beyond a year [45,46]. The longest duration reported for the development of distant metastases is 12 years.

In the context of chemotherapy planning for our patient, the multidisciplinary team (mdt) carefully considered various factors to optimize treatment outcomes while ensuring patient convenience and compliance. Given the operational constraints of the day care centre, where extended stays for chemotherapy administration are impractical, and acknowledging potential challenges in ensuring timely administration of ifosfamide and mesna on consecutive days, the mdt made a strategic decision to administer adriamycin and cyclophosphamide (ac) as part of the treatment protocol.

This decision was motivated by the ease of administration associated with ac, its shorter duration of infusion, and the elimination of the need for mesna. The rationale extends beyond mere logistical considerations; it considers the critical aspect of patient compliance, recognizing the potential difficulty in ensuring patient adherence to a more complex and prolonged chemotherapy regimen.

Importantly, despite the modification in the chemotherapy regimen, the patient responded well, affirming the efficacy of the adapted treatment approach. This positive response reinforces the notion that personalized adjustments to treatment plans, guided by a patient-centric approach, can yield successful outcomes. This case underscores the importance of not only clinical considerations but also practical aspects in achieving an optimal balance for effective cancer care.

IV. Conclusion:

In conclusion, the presented case sheds light on the intricate challenges surrounding the management of malignant phyllodes tumors, particularly when patients arrive with advanced-stage disease and limited prior interventions. This 56-year-old female, hailing from north lakhimpur, sought care with established distant metastases, having undergone wide local excision elsewhere without subsequent adjuvant treatments or insights into the implications of close margins on histopathological examination. Despite the absence of prior surgical interventions at our centre and the lack of awareness regarding the necessity of adjuvant measures, a comprehensive therapeutic approach, combining palliative radiation and a modified chemotherapy regimen, demonstrated notable efficacy. The positive response observed in the patient, despite the intricacies surrounding prior treatments and information gaps, underscores the adaptability of therapeutic strategies. The case emphasizes the critical need for enhanced communication and collaboration across healthcare providers to ensure a continuum of care for patients with rare malignancies. As we navigate the evolving landscape of oncology, this case prompts reflection on the importance of patient education and a multidisciplinary approach in optimizing outcomes for those presenting with advanced stage phyllodes tumors.

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